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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JACQUES DUMAS, BERND RIEDL, UDAY KHIRE, ROBERT N. SIBLEY, HOLIA HATOUM-MOKDAD, MARY-KATHERINE MONAHAN, DAVID E. GUNN, TIMOTHY B. LOWINGER, WILLIAM J. SCOTT, ROGER A. SMITH, and JILL E. WOOD

Appeal 2008-3379
Application 09/838,286
Technology Center 1600

Decided[1]: February 10, 2009

Before DEMETRA J. MILLS, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 CFR § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating diseases mediated by p38. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"The mitogen-activated protein (MAP) kinase family is made up of a series of structurally related proline-directed serine/threonine kinases which are activated either by growth factors . . . and phorbol esters . . . or by IL-1, TNFα or stress (p38 . . .)" (Spec. 1:32-34). The Specification teaches that "inhibition of p38 has been shown to inhibit both cytokine production (eg., TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (eg., MMP-1, MMP-3) *in vitro* and/or *in vivo*" (Spec. 2, ll. 11-13). According to the Specification,

> Inhibitors of p38 are active in animal models of TNFα production, including a muirne [sic, murine] lipopolysaccharide (LPS) model of TNFα production. Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Fruend's [sic, Freund's] adjuvant-induced arthritis in the rat.

(Spec. 5, ll. 20-26).

The Claims

Claims 50 and 52-56 are on appeal. We will focus on claim 50, which is representative and reads as follows:

> 50. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:
>
> A- D- B (I)
>
> or a pharmaceutically acceptable salt thereof, wherein
>
> D is -NH-C(O)-NH-,
>
> A is a substituted t-butylpyridinyl, unsubstituted t-butylpyridinyl, substituted (trifluoromethyl)pyridyl, unsubstituted (trifluoromethyl)pyridyl, substituted isoquinolinyl, unsubstituted isoquinolinyl, substituted quinolinyl or unsubstituted quinolinyl, and
>
> B is a substituted or unsubstituted, phenyl naphthyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl or a bridged cyclic structure of the formula $-L(ML^1)_q$, wherein q is an integer of 1-3, and L^1 and L are each independently thiophene, substituted thiophene, phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, quinolinyl substituted quinolinyl, isoquinolinyl or substituted isoquinolinyl and M is -O-, $-CH_2-$, -S-, -NH-, -C(O)-, $-O-CH_2-$or $-CH_2-O-$, with cyclic structure L bound directly to D,
>
> wherein the substituents for A are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3 and each W is independently selected from the group consisting of
>
> C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having at least a five cyclic members and 0-3 heteroatoms selected from N, S and O; C_{2-10} alkenyl, CH_{1-10} alkenoyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from

O, N and S, C_4-C_{24} alkheteroaryl having at least 5 cyclic members and 1-3 heteroatoms selected from O, N and S;

substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from N, S and O; substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_{6}-C_{14} aryl, substituted C_{7}-C_{24} alkaryl, substituted C_{7}-C_{24} aralkyl, substituted C_3-C_{12} heteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S, substituted C_4-C_{24} alkheteroaryl having at least 5 members and 1-3 heteroatoms selected from O, N and S,

-CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently selected from hydrogen, C_{1-10} alkyl, CH_{1-10} alkoxy, C_{2-10} alkenyl, C_{1-10} alkenoyl, up to per halosubstituted C_{1-10} alkyl, up to per halosubstituted C_{1-10} alkoxy, up to per halosubstituted C_{2-10} alkenyl and up to per halosubstituted CH_{1-10} alkenoyl, C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_3-C_{10} cycloalkyl having at least 5 cyclic members and 0-3 heteroatoms selected from O, S and N, up to per halo substituted C_6-C_{14} aryl and up to per halo substituted C_3-C_{10} hetaryl having at least 6 cyclic members and 0-3 heteroatoms selected from O, S and N,

where W is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, and $-NR^7C(O)R^{7'}$, wherein R^7 and $R^{7'}$ are independently as defined above;

wherein the substituents for B are selected from the group consisting of halogen, up to per-halo, and J_n, where n is 0-3 and each J is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^{7'}$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^{7'}$, $-NR^7C(O)OR^{7'}$, $-NR^7C(O)R^{7'}$, with each R^7 and $R^{7'}$ independently as defined for W above, C_{1-10} alkyl,

CH_{1-10} alkoxy, C_{3-10} cycloalkyl having at least five cyclic members and 0-3 heteroatoms, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-14} aryl, C_{3-12} hetaryl having at least a five cyclic members and 1-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_{7-24} alkaryl, C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having at least a five-members and 0-3 heteroatoms selected from N, S and O, substituted C_{2-10} alkenyl, substituted C_{1-10} alkenoyl, substituted C_6-C_{14} aryl, substituted C_{3-12} hetaryl having at least five cyclic members and 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} alkaryl, substituted C_{7-24} aralkyl and substituted C_4-C_{23} alkylheteroaryl having at least six members and 1-3 heteroatoms selected from O, N and S,

where J is a substituted group, it is substituted by halogen, up to per halo, or by one or more substituents independently selected from the group consisting of-CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^{7'}$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^{7'}$, $-NR^7C(O)R^{7'}$, and $-NR^7C(O)OR^{7'}$, with R^7 and $R^{7'}$ as defined above for W.

The Art

Chialda et al., *Inhibitors of mitogen-activated protein kinases differentially regulate costimulated T cell cytokine production and mouse airway eosinophilia*, 6 RESPIRATORY RES. 1-19 (2005).

Kapoun et al., *TGFβR1 kinase activity, but not p38 activation is required for TGFβR1-induced myofibroblast differentiation and pro-fibrotic gene expression*, MOLECULAR PHARMACOLOGY FAST FORWARD (2006) (Abstract only).

Marc Feldmann, *Pathogenesis of arthritis: recent research progress*, 2 NATURE IMMUNOLOGY 771-773 (2001).

Joseph V. Simone, *Oncology – Introduction*, in CECIL TEXTBOOK OF MEDICINE 1004-1010 (J. Claude Bennett and Fred Plum ed., 1997).

Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 51, 57, 58 (1996).

Dumas et al., *Discovery of a New Class of p38 Kinase Inhibitors*, 10 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 2047-2050 (2000).

Blink et al., *p38 Mitogen-Activated Protein Kinase Inhibition Increases Cytokine Release by Macrophages In Vitro and During Infection In Vivo*, 166 J. IMMUNOLOGY 582-587 (2001).

Trisha Gura, *Systems for Identifying New Drugs are Often Faulty*, 278 SCIENCE 1041-42 (1997).

Johnson et al., *Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials*, 84 BRITISH J. CANCER 1424-1431 (2001).

The Issues

A. The Examiner rejected claims 50 and 52-56 under 35 U.S.C. § 112, first paragraph as enabled for treating rheumatoid arthritis, osteoarthritis and septic arthritis with the compound of formula I but not reasonably enabled for "a method of treating a disease mediated by p38 within a host" with the compound of formula I (Ans. 4-16).

B. The Examiner rejected claims 50 and 52-56 under the judicially created doctrine of double patenting over claims 17-24, 26, and 30-32 of copending U.S. Application No. 09/776,935, and over claims 1, 3, 4, and 7-11 of copending U.S. Application No. 10/086,417 (Ans. 16-17).

A. 35 U.S.C. § 112, first paragraph enablement

The Examiner finds that:

> the specification, while being enabling for treating the specific disease mediated by p38 (e.g., rheumatoid arthritis, osteoarthritis and septic arthritis) by administration of the specific compounds of the Formula I (e.g., 4-ter-Butyl-2-

> pyridyl ureas), does not reasonably provide enablement for "a method of treating a disease mediated by p38 within a host" or "the treatment of a disease other than cancer" with the administration of "a compound of Formula I".

(Ans. 4.)

Appellants contend "[n]o evidence has been presented which even suggests that any compounds of this invention, as inhibitors of p38, would not be effective in treating the diseases defined by the functional language. Furthermore, no evidence has been presented of the 'undue experimentation,' allegedly necessary to practice the invention commensurate in scope with the claims" (App. Br. 3). Appellants contend that "one of ordinary skill in the art, by performing the same or similar tests, can, by routine experimentation, determine the activity levels of each of the claimed compounds in treating various p38 mediated diseases" (App. Br. 5).

In view of these conflicting positions, we frame the enablement issue before us as follows:

Did the Examiner err in finding that it would have required undue experimentation to treat a disease mediated by p38 by administering a compound of formula I?

Findings of Fact (FF)

Breadth of the Claims

1. The Examiner finds that the "claimed invention is directed to a method for the therapeutic treatment of all types of diseases mediated by p38 including cancer (claims 50, 52-54) or all types of diseases mediated by p38 other than cancer (claim 55), comprising administering said compounds represented by the Formula I" (Ans. 9).

2. The Examiner finds that invention comprises treating "multiple complex disorders having unrelated manifestations" (Ans. 9-10). The Examiner finds that "the scope of the instant claims encompasses over 100 different types of diseases that may be related to p38 pathway mechanism" (Ans. 13). Among the many diseases listed in the Specification are inflammatory diseases (Spec. 2, l. 17), asthma (Spec. 2, l. 31), and tuberculosis (Spec. 4, l. 15).

Presence of Working Examples

3. The Specification teaches that the "*in vitro* inhibitory properties of compounds were determined using a p38 kinase inhibition assay" (Spec. 74, ll. 9-10). The Specification states that "[a]ll compounds exemplified displayed p38 IC_{50}s of between 1 nM and 10 μM" (Spec. 75, l. 3).

4. The Specification teaches that the "*in vivo* inhibitory properties of selected compounds were determined using a murine LPS induced TNFα production *in vivo* model" (Spec. 75, ll. 6-7). However, no specific information regarding the values of inhibition for any specific compound is present in the Specification.

Amount of Direction or Guidance Presented

5. The Specification teaches that "[b]ecause inhibition of p38 leads to inhibition of TNFα production, p38 inhibitors will be useful in treatment of the above listed diseases" (Spec. 4:30-31).

6. The Examiner finds that the "specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of [the] disease condition[s] encompassed by the instant claim" (Ans. 13).

State of the Art and Unpredictability of the Art

7. The Examiner finds that "the efficacy of the claimed compounds in treating all complex disease[] condition[s] by all of [the] compounds encompassed by the instant invention cannot be predicted . . . a priori" (Ans. 16).

8. Chialda teaches that "the MAPKs ERK and JNK may be suitable targets for anti-inflammatory therapy of asthma, whereas inhibition of p38 seems to be an unlikely target" (Chialda, abstract).

9. Chialda teaches that "[w]e found, that the p38 inhibitor was not effective . . . . The p38 inhibitor SB203580 did not affect airway inflammation in our model. Conflicting data about the action of p38 inhibitors in asthma models have been reported in the literature" (Chialda 16, col. 2).

10. Kapoun teaches that "SD-208, but not SD-282, [the p38 inhibitor] inhibited TGF^{β}-induced: SMAD signaling, myofibroblast transformation, and collagen gel contraction. Furthermore, we extended our findings to a rat bleomycin-induced lung fibrosis model, demonstrating a significant decrease in the number of myofibroblasts at fibroblastic foci in SD-208, but not SD-282 treated animals" (Kapoun, abstract).

11. Blink teaches that "we observed increased cytokine production in mouse models of pneumococcal pneumonia and tuberculosis accompanied by severely reduced bacterial clearance. This apparent inefficacy of p38 MAPK kinase inhibition in reducing cytokine release in infectious disease, as well as its immune-compromising action, suggest that

targeting p38 MAPK may not be a suitable anti-cytokine strategy in patients with such disease or at risk for infection" (Blink, abstract).

12. Blink teaches that "these findings highlight the uncertainty with respect to the role of p38 MAPK in cytokine production in general and emphasize the need for in vivo assessment of the usefulness of p38 MAPK inhibition as an anti-cytokine inflammatory strategy" (Blink 582, col. 2).

13. Feldmann teaches that "[d]espite the fact that drugs blocking p38 are effective in animal models, human studies so far have been hindered by drug toxicity" (Feldman 772, col. 3).

14. Gura teaches that "'[t]he fundamental problem in drug discovery for cancer is that the model systems are not predictive at all,' says Alan Oliff" (Gura 1041, col. 1).

Quantity of Experimentation necessary

15. The Examiner finds that "one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention" (Ans. 13).

Principles of Law

"In order to satisfy the enablement requirement of section 112, an applicant must describe the manner of making and using the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art ... to make and use the same ...." 35 U.S.C. § 112, para. 1." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the

> quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention and no such evidence or scientific reasoning is present in the instant rejection. *See In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

Analysis

Applying the *Wands* analysis, the claim is broadly drawn to the treatment of any disease mediated by p38, including asthma, tuberculosis, and general inflammatory diseases (FF 1-2). The Specification has two examples: a first example which shows that the compounds of formula I inhibit the p38 kinase and a second example which states, but does not provide any discussion or evidence of, an impact on TNFα (FF 3-4). The Specification does not explain or exemplify any specific p38 inhibitor which will function to treat any one of the specific conditions encompassed by claim 50 (FF 5-6).

The art cited by the Examiner provides extensive evidence of the unpredictability of p38 inhibitors in treating diseases, including diseases expressly listed in the Specification (FF 7-14). In particular, Chialda teaches that the effect of p38 on asthma is disputed in the literature, which is the

essence of unpredictability (FF 9). Feldman teaches that the p38 inhibitors have toxicity issues (FF 13). Blink states that "these findings highlight the uncertainty with respect to the role of p38 MAPK in cytokine production in general and emphasize the need for in vivo assessment of the usefulness of p38 MAPK inhibition as an anti-cytokine inflammatory strategy" (Blink 582, col. 2; FF 12). The Examiner notes that large quantities of experimentation would be required to determine efficacy (FF 15).

Balancing the *Wands* factors, we agree with the Examiner that undue experimentation would have been required to *use* the invention of claim 50 over the entire scope of treating any disease mediated by p38 within a host. The Specification only teaches methods of making the compounds of formula I with no teaching or examples of specific diseases on which the compounds are predicted to function (FF 1-4). There is significant evidence of unpredictability (FF 7-14) and little guidance in the specification (FF 5-6). We find that using the method of the claim reasonably requires undue experimentation.

We are not persuaded by Appellants' argument that "no evidence has been presented of the 'undue experimentation' allegedly necessary to practice the invention commensurate in scope with the claims" (App. Br. 3). In fact, the Examiner has provided abundant evidence that treatment of disease with p38 inhibitors is unpredictable (FF 7-14) and that the Specification provides insufficient guidance to address the concerns of the art (FF 1-4). While Appellants attempt to specifically rebut the teachings of each of the references cited by the Examiner, the references demonstrate the

unpredictability of the art. In fact, the conflict between Chialda and Duane[2][3] regarding whether p38 inhibitors treat asthma (see App. Br. 4) supports the conclusion of unpredictability, since the art shows different results for different p38 inhibitors (FF 8-9).

We also do not find persuasive Appellants' argument that "it would at most involve routine experimentation if any at all, for one of ordinary skill in the art to treat any one of the recited diseases with a compound of this invention" (App. Br. 5). In fact, as shown by the Examiner, it would require undue experimentation to determine which compound within the scope of the thousands or millions of compounds of Formula I would function to treat any of over a hundred different diseases in any specific organism without significant toxicity to that organism (FF 1-15).

Appellants have simply conjectured that every disease associated with TNFα production will be susceptible to treatment by p38 inhibitors (Spec. 2, ll. 10-15). "If mere plausibility were the test for enablement under section 112, applicants would obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318,

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[2] Appellants do not list Duane in the Evidence appendix.
[3] Duane et al., *Inhaled p38a Mitogen-Activated Protein Kinase Antisense Oligonucleotide Attenuates Asthma in Mice*, 171 AM. J. RESPIRATORY CRITICAL CARE MEDICINE 571-578 (2005)

1325 (Fed. Cir. 2005). Additionally, the Examiner has demonstrated that for several specific diseases, including asthma, tuberculosis and inflammatory diseases, p38 inhibitors do not function as therapeutic treatments (FF 7-14).

We are not persuaded by Appellants argument that "Appellants need not illustrate the activity of every embodiment to enable the subject matter of claims 50 and 52-56" (App. Br. 8). The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). The evidence of record shows the unpredictability of the relevant art. (FF 7-14).

Moreover, while a claim may encompass some inoperable subject matter, it must encompass some operable matter. As the Federal Circuit has explained, "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." *Atlas Powder Co. v. E.I. du Pont de Nemours*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984)).

Here, as explained, the Specification does not provide persuasive evidence that even a single compound encompassed by formula I is operative in treating a disease other than those found to be within the enabled scope by the Examiner. Additionally, the laboratory data provided does not satisfy the enablement requirement, since the Specification does not provide any laboratory data indicating that the assayed compounds treat any of the specified diseases.

Conclusions of Law

The Examiner did not err in finding that it would have required undue experimentation to treat a disease mediated by p38 by administering a compound of formula I.

B. Provisional Double Patenting rejection

The two U.S. patent applications, 09/776,935 and 10/086,417, regarding which the Examiner applied the provisional obviousness type double patenting rejection, are both currently abandoned. Thus, the double patenting rejection is moot.

SUMMARY

In summary, we affirm the rejection of claim 50 under 35 U.S.C. § 112, first paragraph enablement. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 52-56 as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

LP

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